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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOUGHTLING, RICHARD A	
ART UNIT	PAPER NUMBER
4133	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,815	GULBINS, ERICH	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	4133	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :18 May 2005; 12 January 2007; 16 May 2007.

DETAILED ACTION

1. In a preliminary amendment filed on May 18, 2005, claims 1-18 were cancelled; and claims 19-36 were added. Claims 19-36 are now pending and are examined on their merits, herein.

Information Disclosure Statements

2. Acknowledged is the receipt of three information disclosure statements filed by applicants on: May 18, 2005, January 12, 2007 and May 16, 2007. Information disclosures were entered into the record and considered by the examiner.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 22, 24, 33, and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding the rejected claims, the phrase "in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Objections

3. Claim 23 is objected to because of the following informalities: typographical error in the spelling of the inhibitor desimipramine. Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-32 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections—35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 19-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using pharmaceutical compositions and methods

for treatment of infectious diseases or diseases influenced by infection does not reasonably provide enablement for methods for prophylaxis of infectious diseases or diseases influenced by infection or making the pharmaceutical compositions as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

According to Stedman's Concise Medical Dictionary (1987), the term "prophylactic" is defined as 1) preventive, preventing disease or 2) an agent that acts as a preventive against disease (p. 613, col. 2, lines 35-41); while, "preventive" is defined as 1) prophylactic 2) anything that ***arrests*** the threatened ***onset of disease*** (p. 607, col.2, lines 53-56). Using the common medical definitions of prophylaxis as preventive, applicants' specification fails to provide enough detailed teachings for an artisan to make and use the invention commensurate within the scope of the claims.

The instant claims 19 and 27 are drawn to a method for the prevention of infectious diseases or opportunistic infections by inhibition of sphingomyelinase activity or reduction of ceramide-rich containing membrane rafts. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would

have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The instant invention pertains to a methods and pharmaceutical compositions for prophylaxis or treatment of infectious disease or opportunistic infections.

State of the art: The skilled artisan would view that prophylaxis or prevention of infectious disease or opportunistic infections—totally, absolutely, or permanently, so as to not even occur the first time is highly unlikely.

Relative skill of those in the art: The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art: The skilled artisan would view that the treatment to prevent infectious disease and/or opportunistic infections—totally, absolutely, or permanently, to be unpredictable, and so as to not even occur at the first time is highly unpredictable. According to applicants' specification (¶ [0003]), treatment

of infectious disease caused by viruses or prions is limited to symptomatic therapy because these pathogens lack mechanisms for their own metabolism. As a result, viral or prion pathogens are not susceptible to antibiotic attack; and therefore, response of viral- or prion-initiated infectious disease may be highly variable depending on viral titer, strain infectivity rates, species infected, etc. As admitted by applicant, symptomatic therapies exist, however, therapeutics that attack such pathogens directly and eradicate them was unknown at the time of applicant's invention. As such, *in lieu* of therapeutic development of drugs to arrest disease onset, hence preventive therapeutics, applicants' specification does not enable a skilled artisan to make or use applicants' invention commensurate with the scope of the instant claims.

Amount of guidance provided by the inventor and existence of working examples:

In the instant case, five working examples are disclosed in the specification as filed; and of these, only two include treatment by using inhibitors of acid sphingomyelinase. As shown in the instant Figures 3 and 4, amitriptyline or imipramine (tricyclic antidepressants) inhibits rhinovirus infection as determined by an indirect function—cell death. Because applicant's claim scope is generic to most pathogenic organisms (see claims 19, 27, and 29; and further includes prophylactic therapy (claims 19 and 27), the teachings necessary to give a skilled artisan an ability to be confident that inhibition of acid sphingomyelinase and/or ceramide-rich membrane platforms resulted in the total, absolute, and complete eradication of infectious disease and/or opportunistic infections

in such a way as to totally, absolutely and permanently, so as to not even occur the first time, without undue experimentation—improbable and highly unlikely.

In lieu of any guidance by applicant, undue experimentation would be required of a skilled artisan to determine the conditions necessary, degree of inhibition of acid sphingomyelinase activity, ceramide-rich platform formation, etc. required to impede the onset of an infectious disease.

Finally, by applicant's own admission on the record, "therapy of HeLa cells with anti-ceramide antibodies *almost completely* inhibits infection of the cells with rhinoviruses...approximately 95% inhibition of infection of the cells with the rhinoviruses," was obtained (col. 16, ¶ [0037], lines 1-3 and 7-9). By such an admission, applicant discloses that prophylaxis is in fact not obtainable by the instant invention. Furthermore, the previously discussed studies were conducted *via in vitro* experimentation and that there is no evidence that this is indicative of what would occur *in vivo*. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed

above, to practice the claimed invention herein, a skilled artisan would have to engage in ***undue experimentation*** to test the combinations in the instant claims as to whether prevention of infectious disease and/or opportunistic infections in any organism could be accomplished so totally, absolutely, or permanently, with no assurance of success.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-32 provide for the use of acid sphingomyelinase inhibition or inhibitors, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 19, 24, 26-30 and 34-36 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Grassme et al. (2002; as found in applicant's IDS filed on May 18, 2005).

Instant claims 19 and 24-30 are drawn to methods of prophylaxis or treatment of infectious diseases or opportunistic infections via inhibition of acid sphingomyelinase (ASM) or its product, ceramide. Independent claims 19 and 27 each are drawn to methods of prophylaxis or treatment of infectious disease, and differ by the mechanism of inhibition, whereby claim 19 methods require inhibition of ASM whereas claim 27 methods require that substances which inhibit and thus interfere with assembly of ceramide-rich platforms be utilized (claim 28). Depending from claim 19 methods, the inhibitor is further limited to that of an antibody (claim 24), which is directed to ASM (claim 25) or ceramide (claim 26). The substances used as inhibitors of claim 27 methods are limited to substances such as β-cyclodextrin, nystatin or filipin (claim 28); while, claims 29 and 30 further limit the type of infection (bacterial, viral, parasitic or mycological infectious diseases) or provide specific diseases (AIDS, hepatitis A, rhinoviral diseases, spring-summer meningoencephalitis, rubella, influenza, tuberculosis, meningococcal infections or malaria) which are to be treated.

Claims 34-36 are drawn to pharmaceutical compositions comprising: desimipramine, FGF, β-cyclodextrin, nystatin or filipin or at least one substance derived therefrom and a pharmaceutical carrier (claim 34); utilizing an effective amount of at least one antibody directed against acid sphingomyelinase (claim 35) or ceramide (claim 36).

Grassme et al. teaches that ceramide-rich membrane rafts mediate the clustering of CD40 via an ASM-dependent mechanism that has been previously shown to be involved in the infection of mammalian cells with pathogenic bacteria (p. 304, Discussion, 1st ¶, lines 7-8). To reduce ceramide, monoclonal antibody 15B4 directed to bind ceramide inhibits CD40 clustering (see p. 303, Figure 4C) and anti-ASM is used in Figure 3D and thus anticipates instant claims 35-36 directed to pharmaceutical compositions. Additional evidence for a role of ceramide-rich membrane rafts in CD40 clustering is found in Figure 4D. Drugs such as nystatin, filipin or β-cyclodextrin, which reduce the amount of cholesterol present in the lipid bilayer, also inhibit CD40 clustering (see p. 303, Figure 4D). Note that each was administered to cells. Thus, each of the limitations mentioned in the above rejected claims are clearly taught by Grassme et al. (2002).

8. Claims 19-22, 27, 29 and 33 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hauck et al. (2000; as found in applicant's IDS filed on May 18, 2005).

The independent method of claim 19, is further limited by claims 20-21 by defining the inhibitors of ASM to those of tricyclic or tetracyclic antidepressants (claim 20), which are further limited to imipramine or amitriptyline (claim 21); and limited by the infectious disease type as viral, bacterial, parasitic or mycological (claim 29). Likewise, the independent method of claim 27 drawn to substances, which inhibit formation of ceramide-rich membrane rafts which may also be further limited by claim 29.

Instant claim 33 is drawn to a pharmaceutical composition including an effective amount of at least one substance derived from tricyclic or tetracyclic antidepressants and a pharmaceutical carrier.

Hauck et al. teaches that human phagocytes internalize *Neisseria gonorrhoeae*, a strain of bacteria which causes the venereal disease gonorrhea in man, through activation of acid sphingomyelinase (ASM) following CEACAM receptor activation by the bacteria (p. 260, abstract and introduction 1st ¶, lines 1-3 and lines 13-16). Treatment using the tricyclic antidepressant, imipramine, a drug known to induce proteolytic degradation of ASM (p. 265, 2nd ¶, lines 1-3) was also effective at reducing the percent of cells infected by the bacteria (i.e. internalized, see Figure 2 B-C, pp. 263), which was reversed upon addition of C_{16} ceramide (see Figure 2 D, p. 264). The authors further teach that inhibition of ASM can lead to alterations in the composition of the membrane and that this may impair pathogen internalization (p. 265, 6th ¶, lines 2-6). Thus Hauck et al. teaches each and every limitation present in claims 19-21, 27 and

29. Finally, since Hauck et al. teaches beneficial effects of imipramine to impede the venereal disease gonorrhea, it further anticipates the pharmaceutical composition of instant claim 33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 19-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grassme et al. (2002) as applied to claims 19, 24, 26-30 above and Hauck et al. (2000) as applied to claims 19-21, 27, 29-30 above, and further in view of Claus et al. (2000; as found in applicant's IDS filed on May 18, 2005) and Haimovitz-Friedman et al. (1997).

The instant dependent claims 22-25 and 31-32 further limit the method of claim 19, and dependent claims 31-32 may also be alternatively drawn to the method of claim 27. Applicant's method of claim 19 is drawn to prophylaxis and treatment of infectious disease or opportunistic infections by inhibition of ASM that is further limited by substances derived from tricyclic or tetracyclic antidepressants (claim 22), to the inhibitor desimipramine or FGF or substances derived therefrom (claim 23), inhibitory antibodies (claim 24), which are specific for ASM (claim 25); as well as disease such as cystic fibrosis which is influenced by infections (claim 31) or infectious diseases—swine fever or rinderpest (claim 32).

Grassme et al. and Hauck et al. are relied upon for the reasons described above. However, Grassme et al. and Hauck et al. do not teach the use of desimipramine, the beneficial effects of FGF, antibodies against acid sphyingomyelinase, the infections that affect cystic fibrosis or the diseases—rinderpest or swine fever. Instead, these components are found in Claus et al., Haimovitz-Friedman et al., each of which further examines ASM/ceramide signaling as it pertains to various forms of infectious disease.

Claus et al. teaches the therapeutic value of targeting the second messenger ceramide, which is formed following activation of sphingomyelinases (including ASM). During HIV infection, increased T cell apoptosis mediated by signaling through CD95/APO-1/Fas receptor/ligand system results in activation of ASM and generation of ceramide (p. 187, 1st ¶ lines 10-13; 2nd ¶ lines 1-3, 5-7). Taken together, Claus et al.

teaches, "inhibition of sphingomyelinase by drug-treatment may lead to a reduction of HIV replication as well as apoptosis" (p. 187, 4th ¶ lines 5-7). Further, in chronically HIV-infected cells, utilization of anti-TNF-α antibodies reduced many of the effects of ASM and a synthetic analog of ceramide on virus expression (p. 187, 6th ¶ lines 1-3). Another potential drug therapy available is to inhibit acid sphingomyelinase by treatment with desimipramine, a tricyclic antidepressant or SR33557, an ASM-selective inhibitor (see p. 186 Table 1).

In addition to HIV infection, both acute and chronic inflammatory reactions are known to also utilize sphingomyelinase and ceramide signaling. During a systemic bacterial infection (sepsis), Haimovitz-Friedman et al. teaches that a systemic bacterial infection or circulating levels of lipopolysaccharide (LPS) results in disseminated endotoxic shock characterized by endothelial apoptosis, organ damage and death (see p. 1834, Figure 1 A-B; p. 1835, Table 1). Measurements of ceramide content of intestinal mucosa demonstrate markedly elevated ceramide levels 1 hr after LPS treatment (p. 1834, 2nd ¶ lines 5-16; p. 1835, Figure 2) or TNF-α administration, which was dramatically reduced in the presence of TNF-bp (p. 1835, Figure 3 and 4, respectively). In response to LPS injection, ASM-deficient mice had about 7-fold less apoptosis than wild-type mice and were protected from LPS-induced death (p. 1836, Figure 5). Haimovitz-Friedman et al. also teaches the beneficial effects of basic fibroblast growth factor (bFGF) revealed when administered with LPS. Treatment of mice with bFGF protected wild-type mice from intestinal mucosa apoptosis and LPS-

induced death by preventing TNF-a induced rise in ceramide (p. 1837, Figure 6 A-B and Table 2).

Each of the references described above teaches how various pathogens associated with infectious disease utilize signaling mechanisms, which require sphingolipid metabolism mediated by increased acidic sphingomyelinase activation and generation of the product—ceramide. Pathogens benefit from activation of this signaling system by producing, in the host, a favorable milieu for its reproduction and survival. Because of rapid pathogen evolution and selective-pressure due to antibiotic over-use, the emergences of antibiotic-and antiviral-resistant strains necessitate the identification of new drug targets and alternative therapies. Thus, an artisan seeking to identify new drug targets against infectious disease pathogens would have combined the teachings of Grassme et al. and Hauck et al. thus identifying the acidic sphingomyelinase—ceramide signaling pathway as a good initial target (claims 19 and 27). Finally, one of ordinary skill in the art would further utilize the teachings of drug treatments effective as inhibitors of the ASM/ceramide pathway taught by Grassme et al., Claus et al., and Haimovitz-Friedman et al. to generate the pharmaceutical compositions and methods of treatment of applicant's claimed invention. Using routine experimentation and optimization strategies, one of ordinary skill in the art would have found it *prima facie* obvious to include infections that effect cystic fibrosis, swine fever or rinderpest given that the strategies demonstrated by Clause et al. and Haimovitz-

Friedman suggested that many types of disease could benefit from this therapeutic development.

Conclusion

In conclusion, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling, Ph.D. whose telephone number is 571-272-9334. The examiner can normally be reached Monday to Thursday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Fridays (9 am – Noon).

The Group 1600 fax phone number where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911.

Richard A. Houghtling, Ph.D.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER